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A Follow-Up Study for Estimating the Effectiveness of a Cross-Gender Hormone Substitution Therapy on Transsexual Patients

Kathrin Schlatterer, M.D., Ph.D.,[1] Alexander Yassouridis, Ph.D.,[2] Klaus von Werder, M.D.,[3] Dorette Poland, M.D.,[4] Johannes Kemper, M.D.,[5] and Günter K. Stalla, M.D.[1,6]

This follow-up study was carried out to validate the effectiveness of cross-gender hormone therapy embedded in a multistep treatment concept for transsexual patients. This therapy described in detail by the authors elsewhere and presented briefly below provides cross-gender hormone substitution to obtain an assimilation of secondary sex characteristics to the desired sex as quickly as possible. Personal and social background data of 46 male-to-female (M-to-F) and 42 female-to-male (F-to-M) patients passing through different stages of the treatment concept were included. In the Endocrinological Outpatient Clinic of the Max-Planck-Institute/Munich the effectiveness of cross-gender hormone replacement therapy as well as frequency and distribution of side effects were examined by follow-up examination of endocrinological parameters. Cross-gender hormones were administered either parenterally or orally. Blood samples were collected routinely after 2 to 6 months depending on the duration of hormone substitution and complication rate. The incidence of hyperprolactinemia in estrogen-treated M-to-F transsexuals lies in the range of studies published before, whereas the number of patients developing galactorrhea is significantly lower in our patients. The incidence of thromboembolic events during the time of cross-gender hormone

[1]Max-Planck-Institute of Psychiatry, Department of Endocrinology, Kraepelinstrasse 10, D-80804 Munich, Germany.
[2]Max-Planck-Institute of Psychiatry, Department Biostatistics, Kraepelinstrasse 10, D-80804 Munich, Germany.
[3]Schloßpark Clinic, Humboldt University Berlin, Heubnerweg 2, D-14059 Berlin, Germany.
[4]Richildenstrasse 52, D-80639 Munich, Germany.
[5]Bauerstrasse 15, D-80796 Munich, Germany.
[6]To whom correspondence should be addressed.

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treatment in our patients is negligible. Changes in hematological parameters are observed under cross-gender hormone therapy. With the cross-gender hormone regimen performed by us it is possible to generate less side effects in the treatment of transsexual patients than described before.

KEY WORDS: transsexuality; sex reassignment; cross-gender hormone therapy; side effects; endocrinology.

INTRODUCTION

Gender dysphoric disorders have been known from antiquity onward across national and cultural boundaries. They have been described in classic literature from Heroditus to Shakespeare (Pauly, 1965; Green, 1966). Historically, no difference was made between transsexualism and transvestism due to the lack of technical opportunities for sexual conversion like hormone application and sex reassignment surgery. Beside the extreme solution of castration, clothing and cosmetics were the only tools available for both groups of individuals. A hormonal sex change became feasible after the discovery of the sex hormones early in the 20th century, and their successful synthesis and commercial manufacture in the 1930s. During the last decades in Western Europe and the United States multistep concepts for the treatment of transsexual patients, in which cross-gender hormone application plays the central role, have been developed and continously improved. Our strategy for cross-gender hormone treatment was refined during the follow-up of 129 transsexual patients treated in our neuroendocrinological outpatient clinic over the last 5 years (Schlatterer *et al.*, 1996). Of those patients, 88 have been included in the present study. Treatment concepts, psychosocial characteristics, and endocrinological follow-up data are presented. The data show a small incidence of side effects due to our therapeutic strategy.

MATERIALS AND METHODS

Sample Population

Transsexual patients were seen by the authors in the Endocrinological Outpatient Clinic of the Max-Planck-Institute between 1991 and 1995 inclusively. During that time 129 patients were referred to us. For the purpose of the present study we reviewed the files of these patients and developed a questionnaire for personal data. The patients were also interviewed. Of the 129 patients treated, 88 (46 M-to-F and 42 F-to-M) provided us with

personal information and were therefore included in the present study, 41 patients either refused to take part in the investigation or their addresses could not be ascertained. A complete history for controlled variables and treatment schedules was obtained besides the personal data. Physical examinations were performed regularly.

Cross-Gender Hormone Therapy

The aim of cross-gender hormone therapy in transsexual patients is an assimilation of secondary sex characteristics to the desired sex as quickly as possible by administration of decreased doses of specific hormone recombinants in consecutive time intervals (steps) after beginning therapy. For this purpose F-to-M transsexuals were treated with a 250-mg depot of testosterone applied intramuscularly. Injection intervals varied between 2 weeks in the beginning to 3 to 4 weeks later on. Optimal lifelong therapy was designed individually by regular screening of serum testosterone, while serum estrogen levels were decreasing. Cross-gender hormone therapy for M-to-F transsexuals is more complex. Testosterone synthesis was decreased effectively by application of the antiandrogen cyproterone acetate. In the beginning of therapy we administered a daily dose of 100 mg orally, slowly adapting it to falling serum testosterone levels. Estrogens usually were administered in a two-phase regimen. High-dose pharmacological estrogen was given in the beginning of therapy as an intramuscular depot, generally every 2 weeks. Optimal individual injection intervals were defined according to patient's risk factors, side effects of therapy, and serum hormone levels in intervals of between 1 and 3 months. As soon as secondary sex characteristics had fully developed, therapy was changed from the high-dose application to a lifelong low-dose estrogen substitution therapy. This also has to be carefully monitored and modified if necessary. Antiandrogen therapy at this point is no longer necessary. For more information concerning cross-gender hormone therapy forms, its risks and side effects, see Schlatterer *et al.*, 1996.

Statistical Analysis

Since the majority of the variables considered in the study are of nominal or categorial data structure, analysis of contingency tables was basically used for evaluating the data at hand. Besides the frequency distributions of transsexuals within the levels (categories) of the various variables, tests of significance of the dependence of transsexuality and certain variables

based on the chi-square statistic were performed. (Note: dependent upon the values of the cell frequencies the p values of the chi-square statistic were calculated either exactly or approximately with Monte Carlo simulations.) A nominal level of significance $\alpha = 0.05$ was accepted. Various tests of independence (or tests of homogeneity) were performed at a reduced level of significance (Bonferroni correction), in order to keep the Type I error less or equal to 0.05.

RESULTS

Before dealing with the effects of cross-gender replacement therapy on endocrinological findings the psychosocial background, the medical and drug background as well as the age distribution within each transsexuality group was investigated. We proposed to compare our results with those obtained by other studies. Information obtained by the aforementioned investigation is presented in Tables I-III.

Endocrinological and Side Effects During Cross-Gender Hormone Therapy

The clinical data of our transsexual patients are presented in Table IV. For 12.5% of our transsexual patients, cross-gender hormone therapy at the time of completion of this study was no longer performed. The number of F-to-M transsexuals with no continued therapy was more than the M-to-F ones (M-to-F: 6.5%, F-to-M: 19.04%). The rest (approximately 80%) of our F-to-M transsexual patients received an intramuscular testosterone application therapy (250 mg every 2–3 weeks). Among the 46 M-to-F patients 32% (i.e., 15 patients) were still in the high-dose pharmacological phase of treatment and received a combination therapy of high dose estrogens together with antiandrogens (estradiol 40–100 mg im every 2 weeks together with cyproterone acetate 10–100 mg daily) whereas 4% (i.e., 2 patients) received high-dose estrogen therapy with estradiol 80–100 mg every 2 weeks alone. Of the M-to-F patients 22% still needed antiandrogen therapy when reducing the estrogen doses to 2–8 mg estradiol daily. In 30% of these patients testosterone serum levels had dropped so far that a combination therapy was pointless. They were administered estradiol 2–8 mg daily alone. For different reasons a minority of 2% of our M-to-F transsexual patients received therapy with natural, unconjugated estrogens. The same number of patients was administered a combination of 2 mg cyproterone acetate and 35 μg ethinylestradiol.

Under the hormone therapy 26% of the M-to-F transsexuals showed no side effects, whereas the number of F-to-M transsexuals without side effects was significantly higher (42%). Although some of our patients showed more than one side effect, we present in Table IV the absolute frequency for the incidence of single side effects only. The most common side effect observed by the M-to-F patients was the development of hyperprolactinemia: 24 M-to-F transsexuals showed this symptom and in 4 we also found transient elevated levels of prolactin. These 4 patients perfomed mechanical compression of their breasts. The nonpersisting elevation of prolactin levels could be traced to this manipulation procedure of the breast. The incidence for transient hyperprolactinemia with normalizing levels of prolactin after dose adjustment was in the range of those found in studies already performed for estrogen-treated M-to-F transsexuals. On the other hand we detected no prolactinoma as descibed by other authors (Asscheman *et al.*, 1988, 1989; Kovacs *et al.*, 1994; Gooren *et al.*, 1980). The portion of patients developing galactorrhea (5/40 ≅ 13%) was lower in our study than the corresponding one found by Futterweit (1980). None of our patients developed deep vein thrombosis or embolism during cross-gender hormone therapy performed in our clinic. These side efects are the most severe ones during estrogen therapy and have been seen in many patients (Fortin *et al.*, 1984; Lehrman, 1976). One of our M-to-F patients suffered from iliac vein thrombosis following surgery, another from deep vein thrombosis before starting therapy. Here it was not clear if the patient self-administered high doses of estrogens without medical control. One patient suffered from lung embolism before starting therapy. Here self-administration of estrogens was also difficult to evaluate. One patient suffered from severe varicosis. Therefore in his case we administered very low doses of estrogens under permanent control of blood-clotting parameters. This therapeutic compromise was performed as an exception, because the patient, who proved to be a serious and reliable partner for hormone therapy, insisted on estrogen administration. A closer examination of blood-clotting parameters as a risk assessment for thromboembolic complications (data not shown) revealed for 11 patients 1 single case of pathologically altered parameters under high-dose estrogen therapy. For this purpose we analyzed the prothrombin time, partial thromboplastin time (PTT), antithrombin III, protein C antigen, functional protein C, protein S antigen and APC-resistance.

Interestingly cross-gender hormone therapy had an influence on erythropoesis. In 15 examined estrogen-treated M-to-F transsexuals we found a decrease of hemoglobin compared to levels of women. In 5, F-to-M transexual patients testosterone treatment induced an increase of hemoglobin to levels normally seen in biological men (Fig. 1). These changes correspond to the effects of androgens on erythropoesis as described by

Table I. Absolute and Relative Frequencies of Transsexuals with Various Levels of Social Background

	Transsexuality						
	M-to-F ($n1$ = 46)		F-to-M ($n2$ = 42)		Total ($n = n1 + n2$)		χ^2 test of independence
	Abs. freq.	Rel. Freq. to $n1$	Abs. freq.	Rel. Freq. to $n2$	Abs. freq.	Rel. Freq. to n	
Marital status							—[a]
Single	29	63.04	36	85.71	65	73.86	
Married	12	26.09	5	11.90	17	19.32	
Divorced	5	10.87	1	2.38	6	6.82	
Total	46	100.00	42	100.00	88	100.00	
No. of children							ns
0	35	76.09	39	92.86	74	84.09	
1	6	13.04	2	4.76	8	9.09	
2	2	4.35	1	2.38	3	3.41	
3	2	4.35	–	–	2	2.27	
> 4	1	2.17	–	–	1	1.14	
Total	46	100.00	42	100.00	88	100.00	
Occupation							ns
Employed/civil servant	28	60.87	23	56.10	51	58.62	
Self-employed	5	10.87	1	2.44	6	6.90	
Unemployed	4	8.70	8	19.51	12	13.79	
School apprenticeship/university	5	10.87	9	21.95	14	16.09	
Retired	4	8.70	–	–	4	4.60	
Data not available	–	–	1	–	1	–	
Total	46	100.00	41	100.00	87	100.00	
Siblings							ns
Yes	27	58.70	18	43.90	45	51.72	
No	19	41.30	23	56.10	42	48.28	
Data not available	–	–	1	–	1	–	
Total	46	100.00	41	100.00	87	100.00	

Disorders in siblings							ns
No	21	80.77	14	77.78	35	79.55	
Yes	5	19.23	4	22.22	9	20.45	
Data not available	1	–	–	–	1	–	
Total	26	100.00	18	100.00	44	100.00	
Endocrinological disorders	1		1		2		
Heart/blood circulation system	1		–		1		
Psychiatric disorders	1		3		4		
Neurological disorders	2		–		2		
Disorders in parents							ns
No	37	80.43	32	76.19	69	78.41	
Yes	9	19.57	10	23.81	19	21.59	
Total	46	100.00	42	100.00	88	100.00	
Hirsutism	2		3		5		
Other endocrinological disorders	–		1		1		
Heart/blood circulation system	3		1		4		
Neoplasia	2		4		6		
Psychiatric disorders	2		1		3		
Neurological disorders	1		2		3		

[a]Rejection of the independence hypothesis or significant associations.

Table II. Medical Disorders (Other Than Transsexuality) and Drug Background of Transsexuals Included in the Analysis

	Transsexuality						
	M-to-F ($n1$ = 46)		F-to-M ($n2$ = 42)		Total ($n = n1 + n2$)		χ^2 test of independence
	Abs. freq.	Rel. Freq. to $n1$	Abs. freq.	Rel. Freq. to $n2$	Abs. freq.	Rel. Freq. to n	
Further patient disorders							—[a]
No	24	52.17	29	70.73	53	60.92	
Yes	22	47.83	12	29.27	34	39.08	
Data not available	–	–	1	–	1	–	
Total	46	100.00	41	100.00	87	100.00	
Endocrinological disorders	6		3		9		
Heart/blood circulation system	4		3		7		
Immunological disorders	1		1		2		
Neoplasia	2		–		2		
Infectious diseases	4		–		4		
Dermatological disorders	3		2		5		
Gastroenterological disorders	1		–		1		
Urological disorders	2		–		2		
Hematological disorders	–		1		1		
Ophthalmological disorders	1		–		1		
Neurological disorders	1		1		2		
Psychiatric disorders	4		5		9		
Further drugs							ns
No	39	84.78	33	80.49	72	82.76	
Yes	7	15.22	8	19.51	15	17.24	
Data not available	–	–	1	–	1	–	
Total	46	100.00	41	100.00	87	100.00	

Further drugs							ns
Psychopharmaceutics	1		2		3		
Heart/blood circulation system	3		1		4		
Agents	1		2		3		
Endocrinological agents	–		1		1		
Dermatics	2		2		4		
Analgetics	–		2		2		
Antiallergics	1		–		1		
Antiinfectious agents	–		–		–		
Alcohol							_[b]
Yes	11	23.91	23	54.76	34	38.64	
No	35	76.09	19	45.24	54	61.36	
Total	46	100.00	42	100.00	88	100.00	
Nicotine							ns
Yes	20	43.48	22	52.38	42	47.73	
No	26	56.52	20	47.62	46	52.27	
Total	46	100.00	42	100.00	88	100.00	

[a]Trend.
[b]Rejection of the independence hypothesis or significant associations.

Table III. Age Distribution Within Transsexuality Modus at Diagnosis and at Beginning of Cross-Gender Hormone Therapy

	Transsexuality						
	M-to-F ($n1$ = 46)		F-to-M ($n2$ = 42)		Total ($n = n1 + n2$)		χ^2 test of independence
	Abs. freq.	Rel. Freq. to $n1$	Abs. freq.	Rel. Freq. to $n2$	Abs. freq.	Rel. Freq. to n	
Age at diagnosis							—[a]
< 20	5	11.36	10	25.64	15	18.07	
21–30	18	40.91	23	58.97	41	49.40	
31–40	14	31.82	6	15.38	20	24.10	
41–50	5	11.36	–	–	5	6.02	
51–60	1	2.27	–	–	1	1.20	
> 60	1	2.27	–	–	1	1.20	
Missing	2	–	3	–	5	–	
Total	44	100.00	39	100.00	83	100.00	
Age at beginning of cross-gender hormone therapy							
< 20	3	6.98	3	7.69	6	7.32	—[a]
21–30	16	37.21	26	66.67	42	51.22	
31–40	16	37.21	8	20.51	24	29.27	
41–50	6	13.95	–	–	6	7.32	
51–60	–	–	–	–	–	–	
> 60	1	2.33	–	–	1	1.22	
No therapy performed	1	2.33	2	5.13	3	3.66	
Data not available	3	–	3	–	6	–	
Total	43	100.00	39	100.00	82	100.00	

[a]Rejection of the independence hypothesis or significant associations.

Table IV. Hormone Therapy and Side Effect Occurrences Within the Two Transsexual Groups

	Transsexuality					
	M-to-F ($n1$ = 46)		F-to-M ($n2$ = 42)		Total ($n = n1 + n2$)	
	Abs. freq.	Rel. Freq. to $n1$	Abs. freq.	Rel. Freq. to $n2$	Abs. freq.	Rel. Freq. to n
Cross-gender hormone therapy						
No longer performed	2	4.35	3	7.14	5	5.68
Will not be performed	1	2.17	5	11.90	6	6.82
Testosterone 250 mg im/every 2–3 weeks	–	–	34	80.95	34	38.64
Estradiol 2–8 mg daily	14	30.43	–	–	14	15.91
Estradiol 80–100 mg im/every 2 weeks	2	4.35	–	–	2	2.27
Natural, conjugated estrogens	1	2.17	–	–	1	1.14
Cyproterone acetate 10–100 mg daily + estradiol 40–100 mg/every 2 weeks	15	32.61	–	–	15	17.05
Cyproterone acetate 10–100 mg daily + estradiol 2–8 mg daily	10	21.74	–	–	10	11.36
Ethinylestradiol 35 μg + cyproterone acetate 2 mg	1	2.17	–	–	1	1.14
Total	46	100.00	42	100.00	88	100.00
Side effects of hormone therapy						
No	10	26.32	13	41.94	23	33.33
Yes	28	73.38	18	58.06	46	66.67
Data not available	8	–	11	–	19	–
Total	38	100.00	31	100.00	69	100.00
Hyperprolactinaemia	24		4		28	
Galactorrhea	5		–		5	
Thrombosis/embolism	–		–		–	
Increase of the transaminases	6		4		10	
Acne	–		4		4	
Persistant bleedings	–		3		3	
Headaches	2		–		2	
Concentration problems/sleep problems	–		3		3	

Table IV. Continued

	Transsexuality					
	M-to-F ($n1$ = 46)		F-to-M ($n2$ = 42)		Total ($n = n1 + n2$)	
	Abs. freq.	Rel. Freq. to $n1$	Abs. freq.	Rel. Freq. to $n2$	Abs. freq.	Rel. Freq. to n
Sex reassignment surgery already performed						
No	17	39.53	16	43.24	33	41.25
Yes	24	55.81	20	54.05	44	55.00
Will not be performed	2	4.65	1	2.70	3	3.75
Data not available	3	–	5	–	8	–
Total	43	100.00	37	100.00	80	100.00
Complications due to surgery						
No	20	83.33	15	75.00	35	79.55
Yes	4	16.67	5	25.00	9	20.45
Total	24	100.00	20	100.00	44	100.00
Wound healing problems	2		3		5	
Infections	1		–		1	
Thrombosis	–		1		1	
Urological problems	1		1		2	
Capsule fibrosis of silicone implants	1		–		1	

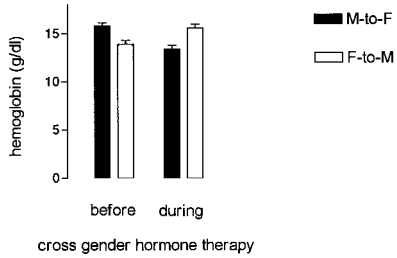

Fig. 1. Effect of cross-gender hormone therapy on hemoglobin levels. Male-to-female transsexuals (M-to-F) treated with estrogens and/or antiandrogens, female-to-male transsexuals (F-to-M) with testosterone.

Kennedy and Gilbertsen (1957). This finding has been tried with varying success as a therapeutic approach for different diseases (Fried *et al.*, 1973, Alexanian, 1969; de Gowin *et al.,* 1970). In view of the erythropoetic effect of androgens, chronic respiratory disorders like emphysema and bronchial asthma are relative contraindications to cross-gender hormone therapy, particularly in heavy smokers.

In the group of F-to-M transsexuals, 3 patients suffered from persistent bleeding which ceased after the application of a high-dose gestagen between the testosterone applications. Three patients also reported concentration and/or sleep problems. Development of acne was seen in 4 patients. In F-to-M transsexuals, acne is one of the most common side effects observed, which often has to be treated with antibiotics (Schlatterer *et al.*, 1996). In the group of M-to-F transsexuals, 2 patients suffered from severe headaches accompanying estrogen medication. For both patient groups (M-to-F and F-to-M transsexuals) a transient increase of liver enzymes was observed, similar to that described by (Meyer *et al.*, 1986; Asscheman *et al.*, 1989). After further diagnostic procedures (screening for hepatitis B and C antigens, ultrasonography of the liver), followed by adjusting and reducing sex hormone doses, these changes in transaminases were no longer detected.

Long-term follow-up studies of cross-gender hormone-treated transsexual patients have not been performed. Interesting objectives would be a systematic evaluation of prevalence of neoplasia and the investigation of an influence of cross-gender hormones on the cardiovascular system. Single case reports of breast cancer in M-to-F transsexuals have been reported previously (Pritchard *et al.*, 1988; Symmers, 1968). Effects of estrogens as part of oral contraceptives on the cardiovascular system are already known (Stadel, 1981; Hannaford *et al.*, 1994; Glashan and Robinson, 1981; Biller

and Saver, 1995; Goh *et al.*, 1995; Damewood *et al.*, 1989; de Marinis and Arnett, 1978).

DISCUSSION

In the last 5 years we have established a cross-gender hormone substitution model for our endocrinological outpatient clinic, embedded in a multistep treatment concept for the transsexual patient (Schlatterer *et al.*, 1996). Here we present data, summarizing our experiences with this therapy. We are by no means certain that our sample of transsexual patients is complete and representative enough to carry out reliable epidemiological calculations. Our findings therefore should be regarded as estimates for an overview of the patient's personal background, endocrinological findings, and the outcome of sex reassignment.

Comparing our findings with others published so far, we first evaluated the psychosocial background (age distribution, marital status, number of children, occupational status, nicotine and alcohol consumption, family background) of our patients as well as the patient's anamnesis. For the most part psychosocial variables of the two groups of our transsexual patients did not differ significantly (see Table I-III), but these results compared to those obtained by other studies reveal some discrepances. With regard to marital status (Table I) the two groups did not show homogeneity in the frequency distribution (χ^2-test, $p < 0.05$). Considerably more M-to-F than F-to-M transsexuals live in marriage, but here also the rate of divorce is higher. Data to date present controversal findings for this feature. Our findings confirm the reports of Hoenig and Kenna (1973) and Kockott and Fahrner (1988). Concerning occupational status, the F-to-M patients show employment patterns similar to M-to-F transsexuals. There are some differences in the frequencies of the single occupational status levels, but their values did not reach statistical significance: 8.7% of our M-to-F patients have already retired. The unemployment rate for F-to-M transsexual patients in our study is higher than that for M-to-F transsexuals. This is in contrast to the findings of Tsoi (1992). In the group of F-to-M transsexuals more patients were still in school, appenticeship, or visited university than in the group of M-to-F transsexuals. Tsoi (1990) has described for Singapore a lower incidence for M-to-F transsexuals to be in higher occupational classes than F-to-M, due to the fact that many M-to-F transsexuals take up service and entertainment jobs which can be graded as skilled or semi-skilled.

One parameter that differs significantly from the studies published is the number of siblings. In our sample as many transsexuals have siblings

as those having none, in contrast to Dixen *et al.* (1984), who published an incidence of being the only child of approximately 12%. In the transsexual patients' parents a high history of psychiatric disorders has been described by Dixen *et al.*, which could not be confirmed by us. We found a weak occurrence of endocrinopathies, cardiovascular problems, neoplastic, and psychiatric-neurological disorders in the parents. Approximately 50% of the M-to-F transsexuals and 30 % of the F-to-M transsexuals show further disorders (see Table II). Endocrinopathies and psychiatric problems are the most frequent disorders, followed by diseases affecting the cardiovascular system, dermatological disorders, and chronic infectious diseases. The relatively high incidence of psychiatric history is consistent with the literature and can be interpreted as evidence of an extreme dissatisfaction that the patients experience in their current, unaccepted gender (Fleming *et al.*, 1981; Pauly 1974).

Previous studies showed a significant number (50%) of associated endocrinopathies in F-to-M transsexuals (Futterweit, 1980). The incidence of chronic infectious diseases like hepatitis B and C as well as HIV infection might possibly be related to the sexual behavior these patients show before their disorder is accepted and treated (same-sex partners, sometimes in a homosexual environment with an increased incidence of sexually transmittable infectious diseases). To a minor extent other disorders have been observed. Approximately 18% of our patients, independent of gender, regularly took other drugs beside cross-gender hormones, Analgesics, psychopharmaceutics, and endocrinological agents are the most frequent. Slightly fewer F-to-M than M-to-F transexuals smoke, whereas the alcohol consumption in F-to-M transsexuals is significantly higher.

The two transsexual groups showed significant discrepances both in the age of diagnosis and in the age at beginning cross-gender hormone therapy (χ^2-test, $p < 0.05$). Most of the patients are diagnosed as transsexual between the age of 21 and 30 years, independently of the biological gender. About 16% of M-to-F transsexuals are diagnosed older than 41 years (Table III). Many of the patients were referred to our clinic by the psychiatrist, followed by the neurologist, the general practicioner, and the internist. As many patients are member of patients' organizations as not.

Hormone replacement therapy was started in our clinic with the same age distribution. The kind of cross-gender hormone therapy was adjusted according to the side effects observed. The incidence of hyperprolactinemia we found in estrogen-treated F-to-M transsexuals (Table IV) lies in the range of studies published before (Asscheman *et al.*, 1988, 1989), whereas the number of patients developing galactorrhea was significantly lower in our patients. None of our patients suffered from a prolactin-producing pituitary adenoma. The incidence of thromboembolic events during cross-

gender hormone treatment in our patients was zero. Changes in hematological parameters were observed under cross-gender hormone therapy. Transient rises in transaminases occurred at a similar frequency as described by other authors (Asscheman *et al.*, 1989; Meyer *et al.*, 1986).

The follow-up of these patients for completed sex reassignment surgery revealed an incidence of problems due to surgery of approximately 20%. Wound healing and urological problems proved to be the most frequent. M-to-F transsexuals were affected slightly more than F-to-M patients, despite better surgical chances for this group. Less than 5% of our transsexual patients refused any surgical intervention. These numbers were independent of biological sex.

With this follow-up study we have been able to demonstrate a low incidence of severe complications occurring due to a specific cross-gender hormone replacement therapy in 88 transsexual patients. Long-term follow-up studies have to be carried out to evaluate further risks of cross-gender hormone replacement therapy like the possible development of neoplasia or long-term effects leading to cardiovascular diseases. Cases of ischemic cerebrovascular diseases accompagnying infertility therapy or cross-gender hormone replacement therapy, as performed in transsexual patients, have been reported (Biller and Saver, 1995). Influences of estrogen and testosterone therapy on lipid/lipoprotein profiles are also described (Goh *et al.*, 1995; Damewood *et al.*, 1989). The design and realization of such studies could help to further improve therapy strategies for transsexuals.

REFERENCES

Alexanian, R. (1969). Erythropoietin and erythropoiesis in anemic man following androgens. *Blood* 33: 564-572

Asscheman, H., Gooren, L. J. G., Assies, J., Smits, J. P. H., and de Slegte, R. (1988). Prolactin levels and pituitary enlargement in hormone treated male-to-female transsexuals. *Clin Endocrinol* 28: 583-588.

Asscheman, H., Gooren, L. J. G., and Eklund, P. L. E. (1989). Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism* 38: 869-873.

Biller, J., and Saver, J. (1995). Ischemic cerebrovascular disease and hormone therapy for infertility and transsexualism. *Neurology* 45: 1611-1613.

Damewood, M. D., Bellantoni, J. J., Bachorik, P. S., Kinball, A. W. Jr., and Rock, J. A. (1989). Exogenous estrogen effect on lipid/lipoprotein cholesterol in transsexual males. *J. Endocrinol Invest.* 12: 449-454.

de Gowin, R., Richard, L., Lavender, A. R., Forland, M., and Charleston, D. (1970). Erythropoietin and erythropoiesis in patients with chronic renal failure treated with hemodialysis and testosterone. *Ann. Intern. Med.* 72: 913-918.

de Marinis, M., and Arnett, E. N. (1978). Cerebrovascular occlusion in a transsexual man taking mestranol. *Arch. Intern. Med.* 138: 1732-1733.

Dixen, J. M., Maddever, H., van Maasdam, J., and Edwards, P. W. (1984). Psychosocial characteristics of applicants evaluated for surgical cross-gender reassignment. *Arch. Sex. Behav.* 13: 269-276.

Fleming, M., Cohen, D., Salt, P., Jones, D., and Jenkins, S. (1981). A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch. Sex. Behav.* 10: 161-170.

Fortin, C. L., Klein, T., Messmore, H. L., and O'Connell, J. B. (1984). Myocardial infarction and severe thromboembolic complications as seen in an estrogen-dependent transsexual. *Arch. Intern. Med.* 144: 1082-1083.

Fried, W., Jonasson, O., and Lang, G. (1973). The hematological effect of androgen in uremic patients. *Ann. Intern. Med.* 79: 823-827.

Futterweit, W. (1980). Endocrine management of the transsexual. *N.Y. State J. Med.* 80: 1260-1264.

Glashan, R. W., and Robinson, M. R. G. (1981). Cardiovascular complications in the treatment of prostatic carcinoma. *Br. J. Urol.* 53: 624-627.

Goh, H. H., Loke, D. F. M., and Ratnam, S. S. (1995). The impact of long-term testosterone replacement therapy on lipid and lipoprotein profiles in women. *Maturitas* 21: 65-70.

Goodwin, W. E., and Cummings, R. H. (1984). Squamous metaplasia of the verumontanum with obstruction due to hypertrophy: long-term effects of estrogen on the prostate in an aging male-to-female transsexual. *J. Urol.* 131: 553-554.

Gooren, L. (1990). The endocrinology of transsexualism: Review and commentary. *Psychoneuroendocrinology* 15: 3-14.

Gooren, L. J. G., van der Veen, E. A., and van Kessel, H. (1980). Modulation of prolactin secretion by gonadal steroids in men. In: MacLeod, R. M., and Scapagnini, U. (eds.), *Central and Peripheral Regulation of Prolactin Function*, Raven Press, New York, pp. 373-375.

Green, R. (1966). Mythological, historical, and cross-cultural aspects of transsexualism. In Benjamin H. *The Transsexual Phenomenon.* The Julian Press, New York.

Hannaford, P. C., Croft, P. R., and Kay, C. R. (1994). Oral contraception and stroke. *Stroke* 25: 935-942.

Hoenig, J., and Kenna, J. (1973). Epidemiological aspects of transsexualism. *Psychiat. Clin.* 6: 65-80.

Kennedy, B. J., and Gilbertsen, S. (1957). Increased erythropoesis induced by androgenic hormone therapy. *New. Engl. J. Med.* 256: 719-726.

Kockott, G., and Fahrner, E. M. (1988). Male-to-female and female-to-male transsexuals: A comparison. *Arch. Sex. Behav.* 17: 539-546.

Kovacs, K., Stefaneanu, L., Ezzat, S., and Smyth, H. S. (1994). Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration. *Arch. Pathol. Lab. Med.* 118: 562-565.

Lehrman, K. L. (1976). Pulmonary embolism in a transsexual man taking diethlstilbestrol. *J. Am. Med. Assoc.* 235: 532-533.

Meyer, W. J., Webb, A., and Stuart, C. A. (1986). Physical and hormonal evaluation of the transsexual patient. A longitudinal study. *Arch. Sex. Behav.* 15: 121-138.

Pauly, I. (1965). Male psychosexual inversion: Transsexualism. *Arch. Gen. Psychiat.* 13: 172-181.

Pauly, I. B. (1968). The current status of the sex change operation. *J. Nerv. Ment. Dis.* 147: 460-471.

Pauly, I. B. (1974). Female transsexualism I and II. *Arch. Sex. Behav.* 3: 487-526.

Pritchard, T. J., Pankowsky, D. A., Crowe, J. P., and Abdul-Karim, F. W. (1988). Breast cancer in a male-to-female transsexual. A case report. *J. Am. Med. Assoc.* 259: 2278-2280.

Schlatterer, K., von Werder, K., and Stalla, G. K. (1996). Multistep treatment concept of transsexual patients. *Exp. Clin. Endocrinol.* (in press).

Stadel, B. V. (1981). Oral contraceptives and cardiovascular disease. *New Engl. J. Med.* 305: 612-618, 672-677.

Symmers, W. C. (1968). Carcinoma of the breast in trans-sexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics. *Br. Med. J.* 2: 83-85.

Tsoi, W. F. (1990). Developmental profile of 200 male and 100 female transsexuals in Singapore. *Arch. Sex. Behav.* 19: 595-605.
Tsoi, W. F. (1992). Male and female transsexuals: A comparison. *Singapore Med. J.* 33: 182-185.